THEORY AND PRACTICE OF IMMUNIZATION

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One of the most significant advances in veterinary medicine in the last 50 years has been the prevention of many infectious diseases that once killed large numbers of dogs and cats. Prevention is possible because it has become technologically feasible to develop safe and efficacious vaccines that are easily administered and offer long-term protection.

The purpose of a vaccination program is to prevent the development of overt clinical disease, either by preventing or limiting infection. If planned properly, vaccine programs can improve animal care by providing a convenient time for a routine health examination. This aspect of the vaccination program has been abandoned by many clinicians but should be considered an important feature of a sound animal health program. The mechanisms by which dogs and cats are protected from infection and disease after vaccination have been and still are the subject of numerous studies by veterinary researchers and clinicians.

It is currently accepted that there are two parts of the specific host defense system:

(1) the **humoral (antibody) system**, consisting of B lymphocytes and the four immunoglobulin classes (IgG, IgM, IgA, and IgE), plus helper cells and, to assist this system, K cells, phagocytic cells, and effector molecules such as complement and properdin and

(2) the **cell-mediated immune (CMI)** system, consisting of T lymphocytes, macrophages, and a number of products of these cells called lymphokines and monokines.

Available information would suggest that vaccine protection is regulated primarily by humoral immunity and secondarily by cell-mediated immunity. This finding would be particularly true if vaccination is known to prevent reinfection, which occurs with effective vaccination and protection against canine distemper, infectious canine hepatitis, and feline panleukopenia. However, when vaccination protects against the development of clinical disease but not against reinfection (which is often the case with feline viral rhinotracheitis, a herpesvirus), cell-mediated immunity and local antibodies play important and perhaps primary roles in preventing disease.

Factors Influencing The Host Defense System

Numerous factors can influence the host defense system and thus effect the immune response to the vaccine. Factors to be considered in designing an effective vaccination program for dogs and cats include the specific immunosuppressive or blocking effect of colostral antibody, the nature of the vaccine, the route of vaccination, the age of the animal, its general nutritional condition, concurrent infections, and drug treatments. These factors will be discussed briefly with respect to the possible influences that each may have on the success of an immunization program.

Maternal Antibody

One of the most common problems associated with vaccination is maternal antibody interference with active immunization. Maternal immunity, a form of passive immunity, has a vital role for neonates. It helps to protect neonates during the critical transition from the protected uterine environment of the fetus to the hostile external environment of the newborn. This transition occurs not only at a time when a neonates immune system is not fully developed but also when a neonate's immune system is naive to virtually all pathogens. Without the acquisition of maternal immunity, a neonate's chances of survival are greatly reduced. However, maternal immunity is not without its negative effects. Maternal antibody interference with immunization is the most common cause of vaccine failure, particularly in weanling

and postweanling animals. It is generally believed that when this interference occurs maternal antibody binds to the vaccine in such a way that the vaccine is cleared from the body before it is able to stimulate an immune response. Because maternal antibody is acquired exogenously and is not actively being replaced, it is gradually depleted as the animal matures.

Maternal antibody is degraded at a *constant* rate. Its retention time in the animal is largely dependent on the class and quantity of antibody acquired at birth. The level of maternal immunity obtained at or around the time of birth is dependent on a number of factors: the immune state of the dam, the amount of colostrum produced, the immunoglobulin (antibody) content of the colostrum, the amount of colostrum ingested and absorbed, and the age of the neonate at the time of ingestion. These factors can cause substantial variation in the amount of maternal antibody that is transferred to newborn animals, even among littermates. The most abundant class of immunoglobulin in colostrum is IgG, which has a 1/2 life of about 14 days, thus 1/2 of the maternal antibody acquired at birth would disappear every two weeks.

Because of these factors, it is difficult to accurately predict the level of maternal antibody for a specific puppy or kitten at the time of immunization. It is possible to obtain a serum sample from a given animal and determine the level of maternal antibody to each pathogen. From this information, the most appropriate immunization time for each agent can be determined. However, the cost and time requirements of such determinations could be prohibitive. The most successful and cost-effective approach to immunizing animals with unknown amounts of maternal antibody is based on multiple vaccinations, with the last immunization occurring at approximately 22 weeks of age for a puppy and approximately 16 weeks of age for a kitten.

By the time an animal reaches these ages, the vast majority (>95%) of animals no longer have levels of maternal antibody sufficient to interfere with active immunization. It is important to note that many of the previous puppy immunization schedules recommend that the last immunization in the series occur at 12 to 16 weeks of age. New information on maternal antibody to canine parvovirus demonstrates the need to extend the last immunization in the series to 20 to 22 weeks of age, so the greatest percentage of puppies possible can be effectively immunized. As many as 20% of dogs at 18 weeks of age have enough maternal antibody to prevent successful canine parvovirus (CPV) immunization. Thus, it is important to recognize that unless the last immunization is given between 20 to 22 weeks of age or later that a certain percentage of the animals will remain unprotected until the next immunization, probably at the yearly booster vaccination. It is possible that under certain conditions where the dam has an exceptional serum titer the level of maternal antibody at 20 weeks of age for a puppy and 14 weeks of age for a kitten may also interfere with the immunization of other canine and feline pathogens, however, this is rare. Thus, for this reason, we recommend that if you want to be certain that there is nos possible interference from maternal antibody the last immunization of the initial vaccination series occur at 22 weeks of age for puppies and 16 weeks of age for kittens. Various immunization programs have recommended initial vaccination ages of 6, 8, or 9 weeks with repeat immunizations at 2-, 3-, 4-, or 6 week intervals. The program that is correct for your practice largely depends on your philosophy and the incidence of disease within your community. Certainly, the more vaccinations an animal receives, within reason, the more likely it will become actively immunized at the earliest possible age and the less likely it will be susceptible when exposed to virulent agents. However, one must weigh the possible risk of infection versus the cost to the client and possible risks to the patient. We believe that a reasonable compromise for puppies would be three to four immunizations given at regular intervals in animals between the ages of 6 and 22 weeks and for kittens two to three immunizations given at regular intervals between the ages of 6 and 16 weeks. Veterinarians frequently blame a vaccine failure on a "bad vaccine." However, it is more likely that the vast majority of vaccine failures, in animals less than 1 year of age, occur as the result of giving the last vaccination when the maternal antibody levels are sufficient to prevent

active immunization.

A substantial problem, especially for CPV, is that virulent virus is able to infect and cause severe disease in animals with levels of maternal antibody that prevent active immunization. There is generally a 2- to 5-week "window of vulnerability" and in heavily CPV contaminated environments as much as a 10 week "window" when an animal can be infected with virulent virus but cannot be successfully immunized. This is of particular concern in some breeding kennels, humane shelters, and pet stores where the level of environmental contamination with CPV is so high that virtually every puppy born within the kennel contracts CPV infection and some develop disease before this can be successfully immunized. In kennels with this problem, the best solution, although often difficult to implement, is to totally remove the puppies from the kennel prior to 4 to 6 weeks of age and not allow them to return until they have completed their full immunization program, at approximately 6 months. It is important that these isolated puppies not have direct or indirect contact with persons or equipment from the contaminated kennel until their immunization program is complete, because CPV is very stable and can persist on fomites for weeks or months.

Maternal antibody interference with canine distemper virus (CDV) immunization is overcome by a unique approach: the development of heterotypic immunity. **Heterotypic immunity** is the production of an immune response to one microorganism by immunizing with a different but antigenically related microorganism. Measles virus (MV) is antigenically related to CDV. When MV is inoculated into a puppy with moderate levels of CDV maternal antibody an immune response is produced that protects the puppy from CDV disease. It is important to realize, when considering the use of MV, that high levels of CDV maternal antibody will also prevent immunization with MV. For this reason, it is not advisable to vaccinate with MV before 6 weeks of age. MV vaccination should be given only once early in the immunization schedule. Multiple immunizations given to older animals may result in high MV maternal antibody titers, which will limit the effectiveness of MV as a heterotypic vaccine for the next generation. MV may be given alone or in combination with CDV vaccine. However, MV is more effective when inoculated alone. Another important and poorly understood aspect of MV vaccine is that MV should only be given intramuscularly.

MV vaccination does not prevent infection with CDV but does prevent the development of clinical CDV disease. This is accomplished by MV vaccination inducing a cross-reactive T-helper cell immunity to CDV. When MV-vaccinated dogs are exposed to CDV, through vaccination or virulent virus, they produce a rapid anamnestic antibody response to CDV. It is this rapid antibody response that prevents clinical CDV disease from developing.

Nature of the Vaccine

Certain questions must be considered if the most effective vaccination program is to be achieved. Is the vaccine virus a modified live or an inactivated virus? If live virus vaccine is used, the vaccine should be handled according to directions supplied by the manufacturer so that it does not become inactive and nonantigenic. Live virus vaccines do not contain enough antigen to immunize the animal unless the virus can infect and replicate in the host. Inactivated vaccines, on the other hand, have a large antigenic mass but in general must be administered several times in order to get an adequate and protective immune response. The question of modified live versus inactivated virus vaccines is often raised. Currently, there are no absolute answers; however, modified live virus vaccines in general are more efficacious and provide a longer period of immunity than inactivated vaccines, but there are notable exceptions. It should be kept in mind that both modified live and inactivated products have a place in the immunization schedule. Does the vaccine contain adjuvant? Adjuvants are added only to killed products to help stimulate protective immunity. Some of the most effective adjuvants cannot be used in vaccines because of the severe reactions

they cause.

To achieve maximum success the entire dose of vaccine should be given as recommended; it should not be divided and given to more than one animal.

Route of Vaccination

The directions specified by the manufacturer should be followed; for example, if an intramuscular route is recommended, do not give the vaccine subcutaneously. Significant differences in host response to certain vaccines exist and are dependent on the route of administration of vaccine. For rabies vaccine it has been reported that the intramuscular route is much more effective than the subcutaneous route. We have also found that the intramuscular route is the only effective route for measles virus. These findings would suggest that the combined canine distemper and measles virus vaccine should be administered intramuscularly and not subcutaneously. For canine distemper and panleukopenia both the subcutaneous and intramuscular routes are effective.

The question of parenteral versus local immunization is one requiring a thorough understanding of the pathogenesis of the disease. Intranasal immunization has the advantage of inducing local antibody as well as local cell-mediated immunity in the respiratory tract. However, if the specific agent replicates in the systemic tissue and not at the local level of the epithelial cells lining the respiratory tract, there is no obvious advantage to local versus parenteral immunization. An example is canine distemper virus, frequently considered to be a respiratory infection but known to replicate initially in lymphoid tissue. In this case there is no advantage to an intranasal product. Panleukopenia is similar, in that the disease is frequently considered an enteric infection, but the virus replicates first in the lymphoid tissue and later infects cells of the gastrointestinal tract. Oral immunization is not only less efficacious than parenteral immunization, we have found oral administration to be without effect unless there is simultaneous intranasal immunization. One should attempt to protect the site of infection; therefore, local immunization may be more efficacious when the primary site of replication is the respiratory (e.g. parainfluenza, FVR, calicious) or gastrointestinal tract (e.g. canine corona virus).

The practice of administering panleukopenia vaccine in food to wild cats maintained in zoos cannot be recommended, since the oral route is ineffective both for the development of antibody and for protection against challenge infection with feline panleukopenia virus.

Age of the Animal

Age is important not only because of persistence of colostral antibody but also because the relative hypothermia that exists during the first week or two of life can cause a state of unresponsiveness for cellular immunity. Optimum body temperatures between 38 and 39°C are very critical for T cell as well as macrophage function in dogs and in cats. Body temperatures less than 37°C are not uncommon in puppies during the first week to 10 days of life, and this lower body temperature is capable of suppressing the CMI system. Because of the interdependence of the B cell system for helper T cells, the antibody response could also be affected by the lowered body temperature. Vaccination during this early period (less than two weeks of age) with live attenuated vaccines is not recommended. Orphaned pups or kittens should receive immune serum in their formula or parenterally to aid in resistance against infection and should not be vaccinated.

There also is evidence to suggest that certain older dogs (seven years of age or more) may have a decreased ability to produce antibody as well as a decreased CMI response due to immune senesence. Annual revaccination during these later years may be important to maintain an active state of immunity. It is assumed that a similar situation exists for cats, but no information is available.

Nutritional State of the Animal

A severely debilitated animal may not respond adequately to a vaccine. The

general state of nutrition should meet minimal recommended standards to ensure that nutritional factors do not interfere with immune responsiveness. If a debilitated dog or cat is vaccinated, vaccination should be repeated when the animal's general condition has improved in order to ensure adequate immunity. In addition, some caution should be exercised when using modified live viruses in a severely debilitated animal, since attenuation is dependent on the host as well as the parasite.

Concurrent Infections

It is important to ensure that animals presented for vaccination are not already incubating the disease. This possibility frequently motivates owners to present their animals for vaccination and may lead to so-called "vaccination breakdowns." A detailed history about the possibility of exposure to infected animals should be obtained and a thorough physical examination should be performed for every patient presented for vaccination in order to minimize this risk.

Other diseases may also be associated with immunosuppression and may potentially interfere with successful vaccination. For example, the general state of T cell suppression present in cases of generalized demodectic mange may interfere with the response to vaccination or, at worst, may contraindicate use of live attenuated vaccines. Likewise, dogs infected with distemper virus develop a generalized T cell suppression four days after infection, and vaccination with other antigens during this period may result in an inadequate immune response.

Feline leukemia virus and Feline Immunodeficiency Virus are known to cause immunosuppression in some cats. The immunosuppression may interfere with protective immunity and may increase the apparent virulence of certain attenuated vaccines.

Drug Treatments

Vaccines should not be given concurrently with immunosuppressive drugs such as cyclophosphamide, azathioprine, methotrexate, and corticosteroids. Corticosteroid treatment in dogs at therapeutic levels does not appear to influence antibody responses to vaccine viruses. However, primary vaccination cannot be highly recommended in dogs receiving steroid therapy. Animals vaccinated while on immunosuppression drugs should always be revaccinated several weeks after the treatment has been discontinued.

High doses of steroid are known to reactivate canine herpesvirus and feline viral rhinotracheitis virus and potentially could cause infection in susceptible contacts.

Immune Serum

Hyperimmune serum, immune serum, or gamma globulin has been described by some in the medical community as "the miracle worker that isn't." The potential of gamma globulin should be re-evaluated and considered for what it is. It must be understood that for gamma globulin or immune serum to be effective it must contain high levels of antibody to the specific organism (e.g., canine distemper or feline panleukopenia) one wants to protect the animal against.

Immune serum or gamma globulin will be of little or no value after the clinical signs of disease are present. However, it will be effective if given immediately after contact exposure with a diseased animal. The situations in which immune serum can be recommended are (1) when an animal enters a humane shelter, pet store, or veterinary clinic; (2) newborn, orphaned pups (give immune serum orally or parenterally); and (3) newborn pups from a bitch without canine herpesvirus antibody but experiencing herpesvirus infection.

Modified Live Vaccines, Killed Vaccines, and Subunit Vaccines

Several types of vaccines are currently used in veterinary medicine: modified live (attenuated), killed (inactivated), and subunit vaccines (Table 1). In **modified live vaccines**, the microorganisms are altered in such a way that they are no longer virulent to the majority of the host species yet retain the antigenic properties that induce a protective immune response. Modified live vaccines may be given locally

or parenterally. Local administration of certain modified live vaccines to the mucous membranes of the eyes, nose, and mouth produces not only a strong systemic immunity but also a local immune response. Local immunity is important when the point of entry of the microorganism and the target organ of the disease are the same (e.g., feline calicivirus). An effective local immune response requires a live replicating vaccine and usually cannot be produced by noninfectious vaccines (killed or subunit). Some live vaccines are not fully attenuated and may require inoculation by an unusual route to produce immunity without causing disease (e.g., feline rhinotracheitis via a parenteral route). Care must be taken when immunizing with this type of vaccine, because aerosolization or environmental contamination may expose susceptible animals, resulting in the development of a mild form of the disease. Modified live vaccines must replicate after inoculation to produce enough antigen to induce an immune response. Thus, any inactivation of a modified live vaccine before or immediately after inoculation will result in vaccine failure. Because modified live vaccines replicate in the host, they more closely resemble virulent viral infections and generally produce a stronger and more durable protective immune response than the noninfectious vaccines (killed and subunit). Modified live vaccines may also induce interferon in the first few days after immunization, providing additional early protection against some virulent viral infections. However, this "better" immune response has a cost: a decrease in vaccine safety. Certain modified live vaccines can induce immunosuppression, may be shed into the environment, and may revert to virulence or cause vaccine-induced disease. Thus, even though modified live vaccines generally provide a better immune response that more closely resembles the natural infection, they are not always the best vaccine on all occasions or for all animals. Fortunately that has been a rare occurrence and modified live vaccines have an excellent safety record.

Killed vaccines are safer than modified live vaccines because they cannot replicate and are unable to cause infectious diseases. However, to induce a protective immune response, killed vaccines require a large antigenic dose, multiple immunizations, and often the use of adjuvants. These factors substantially increase the cost of inactivated vaccines and the probability of local and systemic vaccine reactions. Also, killed vaccines generally produce weaker immune responses with a shorter duration than the immune response produced by modified live vaccines. Sometimes the immune responses they produce lead to immunopathological disease at time of infection rather than protection.

Subunit vaccines are not infectious. Thus, subunit vaccines and killed vaccines have some of the same advantages and disadvantages. However, instead of containing the complete microorganism as found in the modified live and killed vaccines, the subunit vaccine theoretically contains only the components of the microorganism that are necessary to produce a protective immune response. The risk of developing an allergic reaction to nonessential vaccine elements is thus reduced. At present, subunit vaccines are not frequently used in veterinary medicine because of their higher cost and lack of proven efficacy. However, with the advent of recombinant DNA technology and the recent improvements in adjuvants, effective subunit vaccines may become more common. For advantage and disadvantage of types of vaccines and important facts to remember when using each of these see Tables 2, 3.

Table 1

Types of Viral Vaccines

Live-virus vaccines	
Virulent	Delivered by an unnatural route or at a safe age
Attenuated	Naturally occurring or derived by serial passage in eggs or cell culture
	Genetic manipulation possible: temperature-sensitive, cold-adapted, or deletion mutants; or gene reassortants
Non-Infectious Vaccines	
Killed/Inactivated Vaccines	Partially purified suspensions of virus, inactivated by chemical or physical treatment
Protein vaccines	
Subunit	Partially purified protective protein extracted from virions
"Cloned"	Protein derived by recombinant DNA technology, in bacteria, yeast, or mammalian cell line
Synthetic peptide	Critical epitopes of protective protein synthesized chemically
Virus-vectored vaccines	A virus, e.g., vaccinia virus, is used as a vector for the gene specifying the protective antigen

Table 2

Advantages and Disadvantages of Attenuated Live-Virus and Non-Infectious Vaccines

Parameter	Vaccine Type	
	Attenuated live-virus	**Non-Infectious (Inactivated, Killed)**
Route of Administration	Natural[a] or Injection	Injection
Antigen per dose	Low	High or Moderate
Cost	Low	High or Moderate
Number of doses needed	Single[b]	Multiple
Need for adjuvant	No	Yes
Duration of immunity	Many Years to Life	Months or Years
Antibody response	IgG; IgA[d], IgM	IgG, IgM
Cell-mediated response	Good	Uncertain, general no CTL response
Heat liability[e]	Yes[f]	No
Interference	Occasional[g]	No
Side effects	Occasional mild signs	Occasional to frequent local or general reactions
Dangerous in pregnant animals	Some	No (but caution is required since hypersensitivity or stress may cause problem)
Reversion to virulence	Possible	No

[a]Oral or respiratory, in certain cases.
[b]For some live vaccines a second dose may be required
[c]But satisfactory with some inactivated vaccines.
[d]IgA if delivered via oral or respiratory route or if agent replicates locally.
[e]Especially in hot climates
[f]Stabilizers added to vaccine, plus maintenance of "cold chain" delay inactivation.
[g]If administered by oral or respiratory route.

Table 3

Facts to Remember About the Use of Different Types of Vaccines

A.Modified Live Vaccines

(MLV) 1. Provide longer duration and more complete immunity than (Non-Infectious Vaccines).
2. Cellular and secretory immunity.
3. Do not require multiple vaccinations for immunologic memory.
4. Often do not require revaccinating or require fewer revaccinations during life of an animal.
5. Rarely cause hypersensitivities, but may be virulent for certain individual animals or revert to virulence.

B.Killed-Inactivated-Non-Infectious Vaccines

1. Provide short lived systemic immunity.
2. Cellular and secretory immunity poor.
3. Require multiple vaccinations for immunity.
4. Often require re-vaccination to ensure immunologic memory.
5. Often cause hypersensitivity reactions.
6. Cannot cause disease even in immunologically compromised animal.

Proper Use, Storage, and Administration

All vaccines should be stored according to the manufacturer's recommendations. Lyophilized products should be used immediately after reconstitution and not stored for prolonged periods in the reconstituted form. Modified live vaccines are particularly sensitive to improper storage. This type of vaccine relies on vaccine virus replication to generate enough antigen to induce an immune response. Improper storage conditions may result in the inactivation of modified live vaccines and cause vaccine failures. Although modified live vaccines are more sensitive to improper storage, exposing killed and subunit vaccines to excessive heat or light may also result in reduced immunogenicity. To ensure proper immunization, careful attention should be given to the vaccine storage conditions.

It is important that a new needle and syringe be used to administer each vaccine. Reused syringes and needles may contain contaminants that inactivate the vaccine or interfere with immunization. Vaccines should only be administered at the manufacturer's recommended concentration and reconstituted using the diluent provided with the vaccine. Vaccine products from the same or different manufacturers should never be mixed together in one syringe unless specified in the package insert. Vaccine components from different products may interfere with or inactivate each other, resulting in improper immunization.

Adherence to the recommended route of administration is essential. A rabies vaccine labeled "for intramuscular inoculation only" should not be given subcutaneously. For successful immunization to occur, many modified live rabies vaccines require a well-innervated tissue (i.e., muscle). Nerves serve as a target for rabies virus replication. Viral replication is necessary for the production of enough antigen to induce a protective immune response. Thus, inoculation into the subcutaneous connective tissue (low in nerve endings) often leads to vaccine failure unless the vaccine is specifically approved for subcutaneous inoculation.

It is important for veterinarians to follow vaccine recommendations not only to ensure successful immunization but also to limit their liability should an adverse reaction or vaccine failure occur.

Vaccination and Immunosuppression

We recently reported that certain polyvalent vaccines cause immunosuppression, as measured by a significant decrease in an *in vitro* immune function assay, the lymphocyte blastogenesis test (Phillips et al., 1989). When the individual components of the immunosuppressive polyvalent vaccines were inoculated alone into dogs, the immunosuppression did not occur, leading us to believe that the suppression was caused by an interaction between two or more components of the vaccine. We were able to reproduce the suppression of the polyvalent vaccine by combined inoculations of the CDV component and the canine adenovirus type 1 (CAV-1) or canine

adenovirus type 2 (CAV-2) components from various immunosuppressive polyvalent vaccines.

Although the degree of suppression induced by some of the polyvalent vaccines was significant (>80% suppression), it was transitory, persisting for 7 to 10 days. Generally, for immunosuppression to be clinically apparent, it must persist for weeks or months. Thus, vaccination by itself is unlikely to cause detectable adverse effects in an animal. However, under unusual circumstances, even this relatively short duration of lymphocyte suppression may become clinically important, especially if an animal is already in a partially immunosuppressed condition (e.g., nutritional deficiency). Also, it is possible that vaccine-induced immunosuppression may potentiate the severity of a concurrent disease or allow an inapparent infection to become evident.

It is important that results of our study not be misinterpreted. Our results do not suggest that polyvalent vaccines should not be used. All vaccines must be demonstrated safe and efficacious to be licensed. Polyvalent vaccines are efficacious and convenient for both veterinarians and clients. However, vaccination should not be viewed as an innocuous procedure and should be performed in accordance with a manufacturer's recommendations: that is, only *healthy, clinically normal* animals should be vaccinated. It should also be understood that adverse reactions can and will occur regardless of the type of vaccine used.

Polyvalent VS. Monovalent Vaccines

Concern has been expressed about the frequent use of polyvalent vaccines in veterinary medicine. This concern primarily deals with the presumed problems of vaccine interference and antigen overload. Antigen overload occurs when the amount of antigen exceeds the ability of the immune system to respond, and vaccine interference occurs when the inoculation of one vaccine prevents the immune response to another vaccine. There is no scientific evidence that either problem occurs with the currently available canine or feline vaccines. However, as discussed earlier, some polyvalent vaccines have been shown to cause transitory immunosuppression and should be avoided when there is a high potential for concurrent immunosuppression. With monovalent vaccines, concerns about antigen overload, vaccine interference, and vaccine-induced immunosuppression are alleviated but at the expense of convenience and cost.

Immunization of Hospitalized Patients

All animals entering the hospital for elective procedures, boarding, or grooming should have a current vaccination history. If not, they should be immunized at least 10 days before admission. However, an acutely ill patient that requires immediate hospitalization but does not have a vaccination history, in most cases, should *not* be vaccinated for the following reasons: (1) vaccination is not likely to be effective until at least 3 to 7 days after immunization, (2) the immunosuppression of certain polyvalent vaccines may contribute to the current admitting illness, and (3) if the admitting illness has an immunosuppressive component, vaccination may not result in effective immunization or, worse, may result in postvaccinal disease (i.e., postvaccinal distemper encephalitis). Furthermore, if the animal has previously been immunized, it is likely that protective immunity remains. An exception to the foregoing counsel would be an outbreak of a new epizootic disease. In an epizootic outbreak, an acutely ill animal and all animals in contact with the sick animal should be immunized against the agent causing the disease, because the chances of exposure are greatly increased.

Annual Vaccinations

A practice that was started many years ago and that lacks scientific validity or verification is annual revaccinations. Almost without exception there is no immunologic requirement for annual revaccination. Immunity to viruses persists for years or for the life of the animal. Successful vaccination to most bacterial pathogens

produces an immunologic memory that remains for years, allowing an animal to develop a protective anamnestic (secondary) response when exposed to virulent organisms. Only the immune response to toxins requires boosters (e.g., tetanus toxin booster, in humans, is recommended once every 7 to 10 years), and no toxin vaccines are currently used for dogs or cats. Furthermore, revaccination with most viral vaccines fails to stimulate an anamnestic (secondary) response as a result of interference by existing antibody (similar to maternal antibody interference). The practice of annual vaccination in our opinion should be considered of questionable efficacy unless it is used as a mechanism to provide an annual physical examination or is required by law (i.e., certain states require annual revaccination for rabies).

Vaccine Reactions

It is common for an animal receiving its first immunization to have a mild vaccine reaction. At the site of inoculation, a local reaction consisting of a painful inoculation, pruritus, swelling, redness, or abscess formation can occur. These local reactions are more common with inactivated vaccines, because this type of vaccine often contains adjuvants (local irritants) and also a greater amount of antigen than the modified live vaccines. Mild systemic reactions occur, particularly with modified live vaccines, because these vaccines have virus that replicates after immunization. Vaccine virus replication may be viewed as a mild infection that can result in temperature elevation, decreased activity, or increased irritability.

It is important that pregnant animals not be inoculated with any vaccine unless the vaccine has been approved for this use, because fetal resorptions, abortions, or birth defects may result. Inactivated vaccines have been reported to cause problems when given to pregnant dogs, possibly from the stress associated with vaccination or adverse reactions sometimes resulting from these products. Similarly, animals younger than 3 weeks should not receive a modified live vaccine, unless the vaccine has been shown to be safe at this early age.

An occasional dog develops an immune complex disease after being administered CAV-1 vaccine. This condition is called "blue eye," because the affected eye develops a bluish cast in the cornea. The blue is the result of corneal edema, occurring from the deposition of antigen-antibody complexes. This is an immune-mediated (type III hypersensitivity) reaction. The dog usually regains full vision in the affected eye. Because of this adverse reaction, we recommend that dogs be immunized only with CAV-2. CAV-2 vaccine does not cause blue eye and effectively protects against both virulent CAV-1 and CAV-2.

On rare occasions, **anaphylaxis** (type I hypersensitivity) may occur after immunizations. Anaphylaxis usually develops within an hour after immunization, presenting as weakness, dyspnea, vomiting, mucous membrane pallor, collapse, or death. A vaccine component that is most commonly associated with this reaction is the leptospirosis bacterin, although any component including certain of the vaccine adjuvants can cause anaphylaxis. Recently feline vaccines have cause more type I hypersensitivity reactions than seen previously and it is beieved that in certain cases the adjuvants have been a problem and possibly Chlamydia, although this has not been proven. Animals that develop anaphylaxis should not be reimmunized with the same vaccine until the causative component has been identified. Problem animals should be observed at the veterinary clinic for 1 hr after local immunization with all vaccines.

Incomplete vaccine attenuation or vaccination of an immunosuppressed host can result in modified live vaccines causing the disease they are designed to prevent. Examples of this problem are feline respiratory vaccines causing a mild upper respiratory tract disease after immunization and the development of postvaccinal encephalitis subsequent to canine distemper vaccination. An even more alarming example is vaccine induction of clinical rabies (Esh et al., 1982; Pedersen et al., 1978). The reasons why vaccines become virulent are not always known. However, it is important that veterinarians be familiar with these possible outcomes of

immunization and give modified live vaccines only to approved animals that are in good general health and have no clinical indication of immunosuppression.

Most infectious diseases of dogs and cats have been controlled through the use of conventional vaccines. Although not perfect, these vaccines are exceptionally safe and effective. The future challenge will be to continue to improve the safety and efficacy of our current vaccines and to develop new vaccine approaches for diseases that have thus far been resistant to immunization.

Vaccination Failure

A summary of the various factors that can lead to vaccination failure are listed in Table 4. The most common cause of vaccination faiures in pups and kittens is interference of active immunization by maternal antibody.

Minimal Disease Prevention

The following basic recommendations are based on information from a variety of sources, and should be considered our best judgment based on current knowledge of the subject (Tables 5 and 6).

Table 4

*CAUSES OF VACCINATION FAILURE**

Host Factors	Vaccine Factors	Human Error
Maternal Antibody interference	Improper storage	Exposed at time of vaccination
Immunodeficiencies/ Immunosuppression	Inactivated during handling	Improper mixing of products
Pregnancy Age: very young or old	Vaccines do not protect 100% of population	Concurrent use of microbials Simultaneous use of antisera
Pyrexia, hypothermia Incubating disease at time of Vaccination	Disinfectant used on needles and syringes Wrong strain of pathogen	Too frequent administration (<2 week interval) Disinfection of skin?
Drugs: cytotoxic, glucocorticoids	Improper or inadequate adjuvant	Too long between multiple doses during primary vaccination (> 8 weeks) Wrong route of administration
Anesthesia?	Too little antigen	Wrong vaccine

*? = uncertain

Table 5

Vaccines Currently Available for Dogs

Vaccine	Type of Vaccine	Age to Vaccinate
Canine Distemper Virus (CDV)	Modified Live Virus *Killed Virus	First vaccination at 6 to 8 wks of age; second vaccination need not be given until 14 to 16 wks of age, but can be given at 10 to 12 weeks then third vaccination at 14 to 16 weeks.
Measles Virus (MV)/Combined with CDV	Modified Live Virus	Vaccinate at 4 to 8 wks of age, then vaccinate with CDV vaccine at 14 to 16 weeks. There is no need to use in dogs 12 weeks of age or older, use CDV vaccine only! Use when CDV is a known problem such as humane shelters, pet shops, kennels.
Canine Parvovirus Vaccine	Modified Live Virus *Killed Virus	Vaccination schedule same as CDV vaccine, if CPV is a known problem (clinical cases have been seen) give at 8 to 10 wks in addition to 12 to 14 wks. With certain vaccines and for a small percentage of dogs with high maternal antibody it is necessary to give vaccine at 18 to 20 weeks to get active immunity
Infectious Canine Hepatitis (CAV-1) Canine Adenovirus-2 (CAV-2)	**Modified Live Virus *Killed Virus	Vaccination schedule is same as for CDV vaccine and is commonly given with CDV in a combined vaccine. Be sure to use a product with CAV-2.
Canine Coronavirus (CCV)	*Killed Virus	Vaccination schedule is same as for CDV vaccine and is commonly given with CDV in a combined vaccine (I do not recommend)
Rabies Virus	Modified Live Virus	First vaccination at 3 to 4 months of age; revaccinate at 1 year and every 3 years thereafter; if dog is over 4 months of age at first vaccination, revaccinate in 1 year, then once every 3 years. (Some states still may require annual vaccination)
	Killed Virus	First vaccination at 3 to 4 months; second vaccination in 3 to 4 wks; revaccinate at 1 year; revaccinate every three years. (Some states may require annual rabies vaccination.)
Canine Parainfluenza Virus (CPI)	Modified Live Virus *Killed Virus	Give as combined vaccine with canine distemper or the preferred combination is CPI with Bordetella given intranasally. The time of administration can be the same time the CDV product is given.
Canine Leptospirosis	***Killed Bacteria	If first vaccine is at 6 to 8 wks, second vaccine at 9 to 12 wks; if first vaccination at 9 to 12 wks; revaccinate when administering CDV-CAV-2 vaccine at 14 to 16 wks. Revaccinate annually if leptospirosis is a problem in your area. Because duration of immunity is limited and risk is low, this vaccine is not used in certain areas of the U.S.
Canine Bordetella	Modified Live Vaccine ***Killed Bacteria	If first vaccine is at 6 to 8 wks, second vaccine at 10 to 12 wks; if first vaccination at 10 to 12 wks; revaccinate when administering second CDV-CAV-2 vaccine at 14 to 16 wks. The preferred vaccine is to combine with CPI and give intranasally. Annual revaccination is probably necessary for dogs at high risk.
Borrelia-Lyme Vaccine	*Killed Bacteria	First vaccination at 12 or more weeks of age, second dose which is required, should be given 2 to 3 wks. later. Annual revaccination is recommended and should be done in early spring. (I do not recommend this vaccine)

*I do not recommend killed vaccine for this disease, use the modified live product
**I do not recommend any product with CAV-1, only the CAV-2 products should be used due to post-vaccinal uveitis caused by CAV-1 vaccines
***Interval between 2 doses of killed vaccines should not be less than 2 weeks nor more than 4 to 6 weeks

NOTE: In general annual vaccinations are not necessary for most modified live viral vaccines, but they are often recommended.

NOTES

Table 6

A PRACTICAL AND EFFECTIVE VACCINATION SCHEDULE FOR CATS

Vaccine	Type of Vaccine	Age to Vaccinate
Feline Panleukopenia (FLP) (Parvovirus)	Modified Live Virus Inactivated Virus	First vaccination at 6 to 10 weeks of age; second vaccination at 12 to 14 weeks of age. Both modified live and inactivated are excellent and annual revaccination is not necessary, but recommended.
Feline Viral Rhinotracheitis (FVR) (Herpesvirus)	Modified Live Virus Inactive	Given at same time as FPL vaccine and in combination. Annual vaccination is recommended.
Feline Calicivirus (FCV)	MLV Inactivated Virus	Given at same time as FPL vaccine and in combination. Annual vaccination is recommended.
Feline Pneumonitis (Chlaymida)	MLV	First dose at 8 to 10 weeks, second dose at 12 to 14 weeks. I do not recommend use of this vaccine
Rabies	Inactivated	First dose at 12 weeks of age or older. Annual or every three years revaccination recommended.
Feline Leukemia Virus (FeLV) (Retrovirus)	Sub Unit Inactivated	First dose at 8 to 9 weeks, second dose at 11 to 12 weeks (both must be given) (I do not recommend these vaccines for routine immunization and only recommend in exceptional cirucmstances.
Feline Infectious Peritonitis (FIP)	Modified Live	First dose at 12 weeks, second dose at 14 to 16 weeks (I do not recommend the vaccine).